Congenital heart disease : the timing of brain injury

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Association between prenatal Doppler flow patterns, head circumference and postnatal cerebral oxygen saturation in term infants with congenital heart disease

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Abstract

Introduction: It is unknown whether prenatal circulatory alterations persist after birth and affect neonatal cerebral oxygen delivery in infants with congenital heart disease (CHD). We aimed to assess the association between fetal Doppler flow patterns, head circumference (HC) and neonatal cerebral oxygenation in infants with severe CHD.

Material and methods: Cardiac lesions were categorized according to the prenatal pattern of expected oxygen delivery to the brain (low/mixed/normal). Prenatally, we repeatedly assessed HC, pulsatility index of the middle cerebral artery (MCA-PI), umbilical artery (UA-PI), and cerebroplacental ratio (CPR). Postnatally, we assessed HC and cerebral oxygen saturation using near-infrared spectroscopy during the first three days after birth.

Results: In 36 included infants, up to 43% had abnormal Doppler flow patterns at least once during the study. MCA-PI did not correlate with postnatal HC, while UA-PI did (ρ=-0.45, P=0.04). Infants with CHD with low expected cerebral oxygen delivery tended to have lower MCA-PI and CPR and higher UA-PI compared with normal cerebral oxygen delivery. Doppler flow patterns were not associated with postnatal cerebral oxygenation.

Discussion: Fetuses with CHD, particularly those with low expected cerebral oxygen delivery, show some degree of brain sparing. Increased UA-PI seems to correlate with smaller postnatal HC. There are, however, no correlations between prenatal circulatory alterations and postnatal cerebral oxygenation.

Introduction

Up to 50% of infants with congenital heart disease (CHD) suffer from neurodevelopmental impairments later in life.[1] A growing body of evidence suggests that brain injury in these infants might already occur before birth.[2] Several studies have shown that fetuses with CHD have smaller heads compared with healthy controls[3-6] and a high incidence of structural as well as acquired brain lesions.[7-9]

Since fetal cerebral development is a function of delivery of oxygen and substrates, one of the hypotheses is that CHD prenatally leads to circulatory alterations that affect cerebral oxygen delivery and subsequently cause compromised cerebral development.[10] Although it is not possible to measure cerebral oxygen saturation directly during the fetal period, diminished cerebral oxygen supply may be inferred from a number of frequently observed findings. These include a higher pulsatility index in the umbilical artery and a lower cerebral vascular resistance, also called the brain sparing effect, together with a lower cerebroplacental ratio.[11-16] Brain sparing is a compensatory phenomenon that occurs in response to acute or chronic hypoxemia.[16] A recent attempt to estimate cerebral oxygen delivery during pregnancy using magnetic resonance imaging indeed suggested that cerebral oxygen delivery is diminished in fetuses with different types of CHD and that it is associated with smaller brain size.[17]

Many of the prenatal findings in infants with CHD are also present after birth. Infants with CHD are often smaller[18,19], the majority shows signs of cerebral developmental delay[20,21], and many have low cerebral oxygen saturation values.[22,23] Furthermore, up to 53% of infants with CHD show brain abnormalities prior to surgery that are associated with hypoxia and ischemia such as white matter injury and stroke.[24-26] To our knowledge, no study has investigated longitudinally whether circulatory alterations during the fetal period persist after birth and affect neonatal cerebral oxygen delivery. More insight into circulatory alterations in infants with prenatally diagnosed CHD might have the potential to improve neonatal care.

The aim of this study was, therefore, to assess whether prenatal Doppler flow patterns are associated with prenatal head circumference and neonatal cerebral oxygen saturation and extraction in infants with congenital heart disease.

Material and methods

Study population

After Medical Ethical Committee approval, a prospective observational cohort study (registration number: NTR5523) was conducted at the Fetal Medicine Unit (FMU) and the tertiary cardiac and Neonatal Intensive Care Unit (NICU) of the University Medical Center Groningen. All fetuses diagnosed prenatally with CHD requiring NICU admission immediately after birth were enrolled in the study between May 2014 and August 2016. After birth,

cardiac diagnosis was confirmed by a pediatric cardiologist. Infants were excluded from further analyses if born before a gestational age of 36 weeks, if CHD could not be confirmed by postnatal echocardiography or if they had major chromosomal, genetic or structural anomalies that became apparent after birth. Written informed consent was obtained before study enrollment in all cases.

Clustering of CHD

Type of CHD was defined according to the postnatal diagnosis and subsequently categorized based on expected prenatal cerebral oxygen delivery, using a previously published classification.[27] For this classification, expected oxygen saturation of the ascending aorta was used to categorize the infants into three groups: one group with low cerebral oxygen delivery, one group with intracardiac mixing of oxygenated and deoxygenated blood and one group with normal cerebral oxygen delivery.[27]

Prenatal measurements (head biometry and Doppler flow patterns)

Serial biometric parameters including head circumference (HC) were measured at various ultrasound examinations and plotted on national biometric charts.[28] During the same examination, pulsatility index of the middle cerebral artery (MCA-PI) and umbilical artery (UA-PI) were measured and cerebroplacental ratio (CPR) was calculated. To adjust for differences in gestational age, values were converted into z-scores. Z-scores <-1.0 or >1.0 were considered mildly abnormal and z-scores <-2.0 and >2.0 were considered abnormal. For statistical purposes, prenatal measurements were categorized into 5 gestational age periods (20-23 weeks, 24-27 weeks, 28-31 weeks, 32-35 weeks and 36-39 weeks).

Postnatal measurements (head biometry and near-infrared spectroscopy)

To assess neonatal HC, a flexible measuring tape was used and maximum diameter was obtained according to local protocol. Head circumference was assessed the first day after birth and approximately one week after birth to correct for any potential molding at birth.

We used INVOS 5100c near-infrared spectrometers (Somanetics Corporation, Troy, Michigan, USA) in combination with neonatal sensors (Somanetics Corporation) to measure cerebral oxygen saturation (r_cSO_2). Cerebral oxygen saturation (frontoparietal side of the forehead) was measured daily for at least two consecutive hours during the first 3 days after birth. Preferably, measurements were conducted at the same time of the day to reduce the influence of diurnal variations that might exist in r_cSO_2. Simultaneously with r_cSO_2, preductal arterial oxygen saturation (SpO_2) was measured by means of pulse oximetry and fractional tissue oxygen extraction was calculated ($FTOE = (SpO_2-r_cSO_2)/SpO_2$). Data were stored in an online database at a frequency of 0.2Hz. For statistical purposes mean r_cSO_2 and FTOE values per two-hour recording period per day were calculated. As near-infrared spectroscopy

is standard clinical care at our NICU, managing physicians were not blinded to cerebral oxygen saturation values.

Statistical analysis

SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis and GraphPad Prism 5 (GraphPad Software Inc., CA, USA) for graphical display of the results. Data are presented as either median (range) or number (percentage). For graphical display and descriptive purposes, all gestational age periods were used. For statistical analyses, however, we only selected the last available fetal measurement after 32 weeks GA (gestational age periods 4 and 5). The association between Doppler flow patterns, head biometry and cerebral oxygen saturation was assessed for the entire study group using Spearman's correlation coefficient. Furthermore, differences between infants with expected low, mixed or normal oxygen delivery to the brain were assessed using descriptive statistics.

Results

Patient characteristics

Forty-five fetuses with suspected severe CHD were enrolled in the study between May 2014 and August 2016. After birth, nine infants were excluded from further analyses: three because their CHD did not require long-lasting NICU admission, three because of chromosomal or genetic disorders diagnosed after birth (duplication chromosome 7, Turner syndrome, Kabuki syndrome), two because of preterm birth and one infant was stillborn. Gestational age at birth of the 36 included infants was 39.1 (36.6-40.3) weeks and birth weight was 3535 (2100-4120) grams. Patient characteristics are presented in Table 1.

Prenatal measurements

Gestational age during fetal examination ranged from 19.6 to 39.1 weeks. Fetal HC was measured at least once during pregnancy in all 36 infants. There was a large variation in fetal HC z-scores at all five gestational age periods. Overall, the majority of fetuses with CHD had HC z-scores within the normal ranges. Pulsatility index of the MCA or UA-PI were measured in all fetuses and in 31 fetuses the cerebroplacental ratio could be calculated. Forty-three percent of the cases had MCA-PI z-scores of less than -1.00 at least once during pregnancy and 40% had UA-PI z-scores above 1.00 at least once. Twenty percent had MCA-PI z-scores <-2.0 at least once during pregnancy and 23% had UA-PI z-scores above 2.0. The course of prenatal measurements is presented in Figure 1.

Table 1 Patient characteristics

	N = 36
Gestational age at birth (weeks)	39.1 (36.6-40.3)
Birth weight (grams)	3535 (2100-4120)
Male	21 (58)
Type of CHD	
- TGA	9 (25)
- HLHS	4 (11)
- Pulmonary stenosis	1 (3)
- Pulmonary atresia	2 (6)
- Coarctation of the aorta	4 (11)
- Tetralogy of Fallot	4 (11)
- Truncus arteriosus	3 (8)
- Complex	4 (11)
- AVSD	1 (3)
- Tricuspid dysplasia	1 (3)
- DORV	3 (8)
Cesarean section	2 (6)
Apgar at 5 minutes	8 (5-10)
Mortality	7 (19)
MABP day 1	44 (37-51)
MABP day 2	47 (34-56)
MABP day 3	46 (42-54)
Respiratory support day 1 *(n=35)*	
- None/low flow	19 (54)
- CPAP	9 (26)
- NIPPV	1 (3)
- SIMV/SIPPV	6 (17)
Respiratory support day 2 *(n=34)*	
- None/low flow	19 (56)
- CPAP	3 (9)
- NIPPV	2 (6)
- SIMV/SIPPV	10 (29)
Respiratory support day 3 *(n=32)*	
- None/low flow	20 (63)
- CPAP	3 (9)
- NIPPV	2 (6)
- SIMV/SIPPV	7 (22)
Medical treatment	
Prostaglandin E_1 day 1	22 (63)
Prostaglandin E_1 day 2	22 (65)
Prostaglandin E_1 day 3	21 (66)
Sedatives* day 1	8 (23)
Sedatives* day 2	15 (44)
Sedatives* day 3	12 (38)
Placental insufficiency (pathology report)	4 (11)

Data represent either median (range) or number (percentage). CHD, congenital heart disease; TGA, transposition of the great arteries; HLHS, hypoplastic left heart syndrome; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; MABP, mean arterial blood pressure; CPAP, continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; SIMV, synchronized intermittent mandatory ventilation; SIPPV, synchronized intermittent positive pressure ventilation. * Treatment with morphine or midazolam.

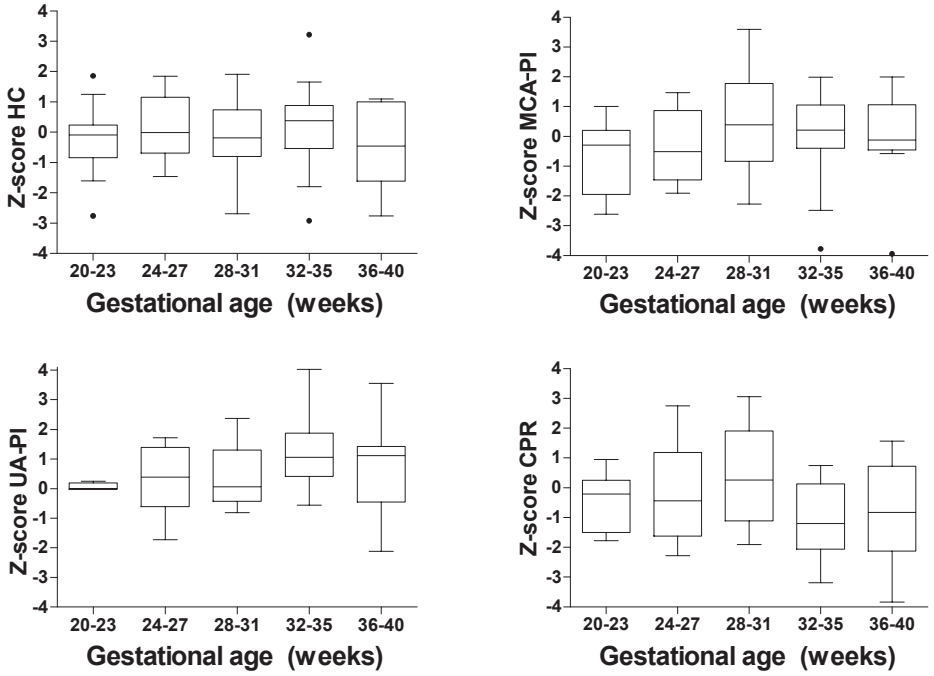

Figure 1 Prenatal head circumference and Doppler flow patterns. Data are shown in box-and-whisker plots. Circles represent outliers. HC, head circumference; MCA-PI, pulsatility index of the middle cerebral artery; UA-PI, pulsatility index of the umbilical artery; CPR, cerebroplacental ratio.

Postnatal measurements

Neonatal HC was measured in 32 neonates. Head circumference at birth was smaller in neonates with CHD in comparison with reference values from a healthy population (-1.22 (-4.01 to 1.16)).[28] This difference was still present one week after birth, when any potential molding would have disappeared (-1.05 (-3.22 to 1.37). During the first 3 days after birth, r_cSO_2 was measured in 35, 34 and 32 infants, respectively. Reasons for missing values after birth were transfer of the neonate to another department/hospital or death. Median r_cSO_2 values during the first 3 days after birth were 61% (32%-89%), 69% (42%-89%) and 70% (52%-91%), respectively. Preductal SpO_2 ranged from 90% (74%-99%) on day 1 to 91% (77%-99%) on day 3. Fractional tissue oxygen extraction was calculated in 33 infants on day 1, 31 infants on day 2, and 30 infants on day 3 and ranged from 0.27 (0.05-0.61) on day 1 to 0.24 (0.02-0.47) on day 3. Neonatal HC, preductal SpO_2, r_cSO_2 and FTOE values are displayed in Figure 2.

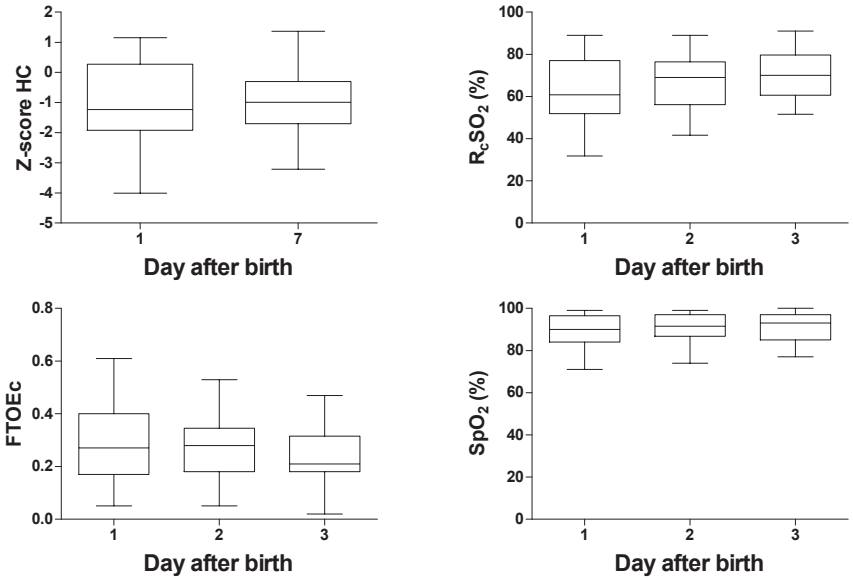

Figure 2 Postnatal head circumference and arterial and cerebral oxygen saturation. Data are shown in box-and-whisker plots. HC, head circumference; r_cSO_2, regional cerebral oxygen saturation; SpO_2, arterial oxygen saturation; FTOEc, cerebral fractional tissue oxygen extraction.

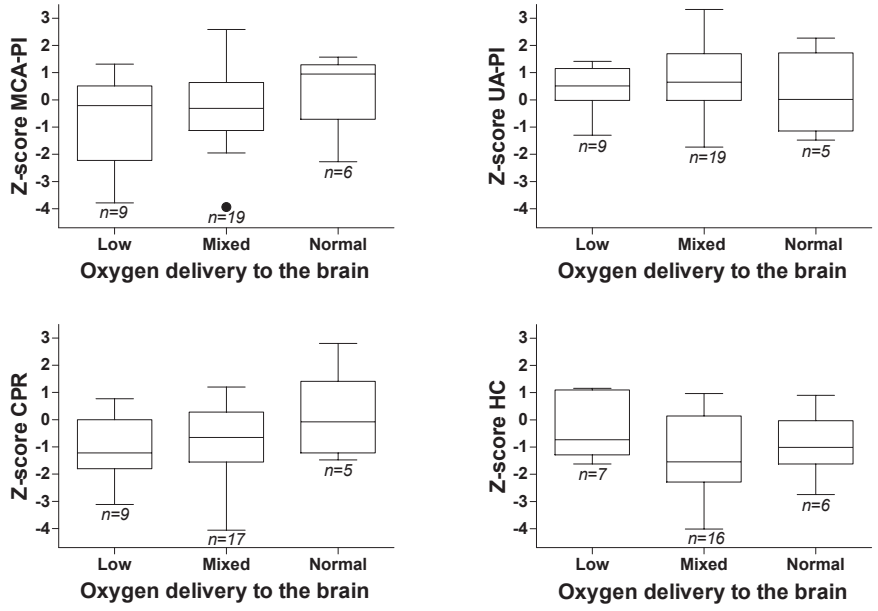

Figure 3 Doppler flow patterns according to cerebral oxygen delivery. Data are shown in box-and-whisker plots. Circles represent outliers. HC, head circumference; MCA-PI, pulsatility index of the middle cerebral artery; UA-PI, pulsatility index of the umbilical artery; CPR, cerebroplacental ratio.

Table 2 Correlations between Doppler flow patterns, head circumference and cerebral oxygen saturation in the entire study group

	MCA-PI	UA-PI	CPR
Prenatal HC	-0.17 (0.44)	-0.36 (0.10)	0.13 (0.57)
HC after birth	0.01 (0.99)	-0.45 (0.04)*	0.34 (0.16)
HC after 1 week	0.28 (0.29)	0.26 (0.29)	0.34 (0.18)
R_cSO_2 day 1	-0.09 (0.69)	-0.01 (0.98)	0.08 (0.70)
R_cSO_2 day 2	0.07 (0.75)	-0.09 (0.68)	0.06 (0.81)
R_cSO_2 day 3	0.11 (0.62)	-0.06 (0.79)	0.06 (0.81)
FTOEc day 1	0.11 (0.62)	-0.10 (0.65)	0.18 (0.41)
FTOEc day 2	-0.24 (0.31)	-0.04 (0.89)	0.02 (0.99)
FTOEc day 3	-0.22 (0.36)	-0.01 (0.97)	-0.06 (0.81)

Doppler flow patterns: 32 to 40 weeks. Data are presented as correlation coefficient (*P*-value). HC, head circumference; r_cSO_2, cerebral oxygen saturation; FTOEc, cerebral fractional tissue oxygen extraction; MCA-PI, pulsatility index of the middle cerebral artery; UA-PI, pulsatility index of the umbilical artery; CPR, cerebroplacental ratio. * indicates *P*-value <0.05.

Spearman's correlation coefficient for the entire study group

In the entire study population, UA-PI correlated negatively with HC at birth (ρ=-0.45, *P*=0.04), while MCA-PI and CPR did not correlate with prenatal or postnatal HC. No significant correlations could be demonstrated between Doppler flow patterns and cerebral oxygen saturation and extraction during the first 3 days after birth in the entire study population. Spearman's correlation coefficients in the entire study population are presented in Table 2.

Differences between CHD categories

Based on expected prenatal cerebral oxygen delivery according to the type of cardiac defect, 9 infants were assigned to low cerebral oxygen delivery group, 21 infants to mixed cerebral oxygen delivery group and 6 infants to normal oxygen delivery to the brain group (Supplemental Table 1). As these subgroups were too small for statistical analyses, we used descriptive statistics to show trends in infants with either low, mixed or normal cerebral oxygen delivery (Figure 3). Pulsatility index of the MCA was lowest in infants with low cerebral oxygen delivery (-0.21 (-3.78 to1.32)) and the highest in infants with normal cerebral oxygen delivery (1.02 (-2.27 to 1.57)). Pulsatility index of the UA showed a tendency to be lower in infants with normal cerebral oxygen delivery (0.02 (-1.48 to 2.27)) in comparison with infants with low or mixed cerebral oxygen delivery (0.51 (-1.30 to 1.40) and 0.65 (-1.74 to 3.32), respectively). Cerebroplacental ratio was the lowest in infants with low cerebral oxygen delivery (-1.22 (-3.11 to 0.77)) and the highest in infants with normal cerebral oxygen delivery (-0.08 (-1.48 to 2.80)). Infants with mixed cerebral oxygen delivery had the smallest HC at birth (-1.54 (-4.01 to 0.97)).

Discussion

To our knowledge, this is the first longitudinal study in infants with CHD addressing the association between fetal Doppler flow patterns, head circumference measurements before and after birth and neonatal cerebral oxygen saturation. Our main findings are that infants with CHD have smaller heads in comparison with healthy infants and that up to 23% show abnormal Doppler flow patterns during pregnancy. These abnormal Doppler flow patterns are especially found in fetuses with CHD with low cerebral oxygen delivery. We were, however, unable to show an association between prenatal circulatory alterations and postnatal cerebral oxygen saturation and extraction.

HC z-scores showed a great variation during pregnancy and, although values showed a tendency to decrease later in pregnancy, median z-scores were around zero, suggesting normal head sizes. In contrast, HC measured at birth and one week later, were significantly smaller compared with normal reference values.[28] Smaller HC in infants with CHD and reduced fetal head growth rate have been previously described.[5,16,18] This process of reduced growth speed may particularly become evident in the late third trimester and could therefore explain the smaller HCs at birth and one week after birth in our study population. Alternatively, the discrepancy between prenatal and postnatal HC z-scores may purely be due to the difference in reference values used for calculating z-scores before and after birth.[28-29]

Of the Doppler parameters, only UA-PI was significantly inversely associated with neonatal HC. This may suggest that fetuses with increased UA-PI suffered from mild degrees of placental insufficiency, implying reduced cerebral oxygen delivery and impaired cerebral growth. Surprisingly, we were unable to find a clear association between cerebral perfusion and head growth, although fetuses with low cerebral oxygen delivery more often showed lower MCA-PI and CPR values. In fact, in our cohort, mildly abnormal (z-score <-1.0) or abnormal values (z-score <-2.0) were recorded at least once during pregnancy in up to 43% and 23% of cases, respectively, which is in line with previous reports.[11-16]

Similarly to our study, Hahn et al. did not find an association between HC and MCA-PI[16] and Jansen et al. did not find differences in head growth rate between fetuses with CHD with low, mixed or normal expected oxygen saturation in the ascending aorta.[27] Head growth may be more dependent on other variables, such as genetic factors that do not influence prenatal cerebral perfusion. Alternatively, hemodynamic changes may be intermittent and therefore less prone to be detected by Doppler measurements performed occasionally. On the other hand occasional low MCA-PI measurements may be purely due to the intrinsic intra-fetal variation. It is in fact known that especially near term cerebral perfusion is very sensitive to changes in fetal activity or sleep-state.[30]

Although prenatal Doppler flow patterns were more often altered in fetuses with expected low cerebral oxygen delivery, there was no association between prenatal cerebral hemodynamics and postnatal cerebral oxygen saturation and extraction. This is at variance with the study of Nagaraj et al. who reported that fetuses with CHD and CPR <1.0 had higher global and regional cerebral blood flow after birth in comparison with fetuses with CHD with CPR >1.0.[31] Also, in intrauterine growth restriction (IUGR), where prenatal hemodynamic adaptations in favor of brain perfusion are constant, circulatory changes persist for the first 3 days after birth.[32] The different behavior in infants with CHD could be due to the fact that prenatal Doppler flow patterns were more abnormal in the IUGR group studied by Tanis et al.[32] Furthermore, the mechanism responsible for circulatory alterations in favor of brain perfusion might be completely different in infants with IUGR compared with CHD. We speculate that in fetuses with CHD increased brain perfusion may be intermittently present and represent a more subtle compensatory mechanism to adjust for lower oxygen saturation due to CHD specific mixing patterns, while in fetuses with IUGR brain sparing is consistently present in response to chronic hypoxemia and starvation due to placental insufficiency.[33]

Another explanation for the lack of association between prenatal Doppler flow patterns and postnatal r_cSO_2 and FTOE might be the effect of transition from fetal to neonatal life. Circulatory and respiratory changes during the transition are associated with differences in cerebral oxygenation, particularly in infants with severe CHD. Additionally, interventions after birth, such as mechanical ventilation or treatment with vasodilatatory Prostaglandin E_1 may have masked the association between prenatal Doppler flow patterns and postnatal r_cSO_2 and FTOE. Furthermore, r_cSO_2 was measured as part of routine clinical care in these infants and therefore not blinded to the attending staff that might have acted on low r_cSO_2 values.

This study has several limitations. First, although we included almost all infants with prenatally diagnosed CHD referred to our FMU between May 2014 and August 2016, the study population was relatively small, owing to the fact that many parents opted to terminate pregnancy. Furthermore, the included fetuses had different types of CHD, each with its own intracardiac oxygen-mixing pattern, resulting in small numbers for each type of CHD. We could confirm that fetuses with CHD associated with impaired cerebral oxygen supply more often show signs of decreased cerebral vascular resistance,[5] but, due to the group size, we were unable to demonstrate significant differences between the various types of CHD. Further research should focus on this aspect. Second, this study was an observational clinical study with inevitable missing values and variation in gestational age at examination. This has prevented multivariate statistical trend analysis. Another important consideration in the interpretation of the results is that both near-infrared spectroscopy and Doppler flow patterns are subject to intra-patient variation.[34] Studies on variability and

reproducibility of Doppler measurements in fetuses with different types of CHD are lacking and should be performed in the future.

In conclusion, in infants with CHD that requires admission to the NICU after birth, prenatal Doppler flow patterns seem to be associated with a late slowing down in fetal head circumference growth that seem to reflect the oxygen-mixing pattern of the cardiac defect. However, prenatal Doppler flow patterns are not associated with postnatal cerebral oxygen saturation or extraction.

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References

1. Marino BS, Lipkin PH, Newburger JW et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012;126:1143-1172.
2. Mebius MJ, Kooi EMW, Bilardo CM et al. Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review. Pediatrics 2017 Jul;140(1):10.1542/peds.2016-4055. Epub 2017 Jun 13
3. Williams IA, Fifer WP, Andrews H. Fetal Growth and Neurodevelopmental Outcome in Congenital Heart Disease. *Pediatr Cardiol* 2015;36:1135-1144.
4. Masoller N, Martinez JM, Gomez O et al. Evidence of second-trimester changes in head biometry and brain perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2014;44:182-187.
5. Ruiz A, Cruz-Lemini M, Masoller N et al. Longitudinal changes in fetal biometries and cerebroplacental haemodynamics in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2017;49:379-386.
6. Zeng S, Zhou QC, Zhou JW et al. Volume of intracranial structures on three-dimensional ultrasound in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015;46:174-181.
7. Brossard-Racine M, du Plessis A, Vezina G et al. Brain Injury in Neonates with Complex Congenital Heart Disease: What Is the Predictive Value of MRI in the Fetal Period? *AJNR Am J Neuroradiol* 2016;37:1338-1346.
8. Brossard-Racine M, du Plessis AJ, Vezina G et al. Prevalence and spectrum of in utero structural brain abnormalities in fetuses with complex congenital heart disease. *AJNR Am J Neuroradiol* 2014;35:1593-1599.
9. Mlczoch E, Brugger P, Ulm B et al. Structural congenital brain disease in congenital heart disease: results from a fetal MRI program. *Eur J Paediatr Neurol* 2013;17:153-160.
10. Donofrio MT, Bremer YA, Schieken RM et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol* 2003;24:436-443.
11. Arduini M, Rosati P, Caforio L et al. Cerebral blood flow autoregulation and congenital heart disease: possible causes of abnormal prenatal neurologic development. *J Matern Fetal Neonatal Med* 2011;24:1208-1211.
12. Kaltman JR, Di H, Tian Z et al. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005;25:32-36.
13. Zeng S, Zhou J, Peng Q et al. Assessment by three-dimensional power Doppler ultrasound of cerebral blood flow perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015;45:649-656.
14. Yamamoto Y, Khoo NS, Brooks PA et al. Severe left heart obstruction with retrograde arch flow influences fetal cerebral and placental blood flow. *Ultrasound Obstet Gynecol* 2013;42:294-299.
15. Szwast A, Tian Z, McCann M et al. Comparative analysis of cerebrovascular resistance in fetuses with single-ventricle congenital heart disease. *Ultrasound Obstet Gynecol* 2012;40:62-67.
16. Hahn E, Szwast A, Cnota J et al. Association between fetal growth, cerebral blood flow and neurodevelopmental outcome in univentricular fetuses. *Ultrasound Obstet Gynecol* 2016;47:460-465.
17. Sun L, Macgowan CK, Sled JG et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation* 2015;131:1313-1323.
18. Rosenthal GL. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. *Am J Epidemiol* 1996;143:505-513.
19. Malik S, Cleves MA, Zhao W et al. Association between congenital heart defects and small for gestational age. *Pediatrics* 2007:e976-82.
20. Sethi V, Tabbutt S, Dimitropoulos A et al. Single-ventricle anatomy predicts delayed microstructural brain development. *Pediatr Res* 2013;73:661-667.
21. Shedeed SA, Elfaytouri E. Brain maturity and brain injury in newborns with cyanotic congenital heart disease. *Pediatr Cardiol* 2011;32:47-54.
22. Kurth CD, Steven JL, Montenegro LM et al. Cerebral oxygen saturation before congenital heart surgery. *Ann Thorac Surg* 2001;72:187-192.
23. Mebius MJ, van der Laan ME, Verhagen EA et al. Cerebral oxygen saturation during the first 72h after birth in infants diagnosed prenatally with congenital heart disease. *Early Hum Dev* 2016;103:199-203.

24. Bertholdt S, Latal B, Liamlahi R et al. Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery. *Eur J Cardiothorac Surg* 2014;45:625-632.
25. Andropoulos DB, Ahmad HB, Haq T et al. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. *Paediatr Anaesth* 2014;24:266-274.
26. Mulkey SB, Swearingen CJ, Melguizo MS et al. Multi-tiered analysis of brain injury in neonates with congenital heart disease. *Pediatr Cardiol* 2013;34:1772-1784.
27. Jansen FA, van Zwet EW, Rijlaarsdam ME et al. Head growth in fetuses with isolated congenital heart defects: lack of influence of aortic arch flow and ascending aorta oxygen saturation. *Ultrasound Obstet Gynecol* 2016;48:357-364.
28. Verburg BO, Steegers EA, De Ridder M et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol* 2008;31:388-396.
29. Talma H, Schönbeck Y, Bakker B et al. Groeidiagrammen 2010. Handleiding bij het meten en wegen van kinderen en het invullen van groeidiagrammen. TNO/VUmc/LUMC. TNO 2010
30. van Eyck J, Wladimiroff JW, van den Wijngaard JA et al. The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in normal pregnancy at 37-38 weeks. *Br J Obstet Gynaecol* 1987;94:736-41.
31. Nagaraj UD, Evangelou IE, Donofrio MT et al. Impaired Global and Regional Cerebral Perfusion in Newborns with Complex Congenital Heart Disease. *J Pediatr* 2015;167:1018-1024.
32. Tanis JC, Boelen MR, Schmitz DM et al. Correlation between Doppler flow patterns in growth-restricted fetuses and neonatal circulation. *Ultrasound Obstet Gynecol* 2016;48:210-216
33. Miller SL, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. *J Physiol* 2016;594:807-823.
34. Sorensen LC, Greisen G. Precision of measurement of cerebral tissue oxygenation index using near-infrared spectroscopy in preterm neonates. *J Biomed Opt* 2006;11:054005.

Supplemental Table 1 Congenital heart disease diagnosis and categorization

NR	Diagnosis	Diagnosis category
1	Pulmonary atresia with intact ventricular septum and ventricular-coronary fistulas	1
2	Transposition of the great arteries with intact ventricular septum	0
3	Critical subvalvular pulmonary stenosis	2
4	Monoventricular heart, transposition of the great arteries, complete atrioventricular septal defect, subvalvular pulmonary stenosis	1
5	Truncus arteriosus type I	1
6	Coarctation of the aorta and ventricular septal defect	2
7	Transposition of the great arteries with intact ventricular septum	0
8	Transposition of the great arteries with ventricular septal defect	0
9	Hypoplastic left ventricle, critical aortic valve stenosis, coarctation of the aorta, hypoplastic aortic arch	1
10	Tetralogy of Fallot	1
11	Transposition of the great arteries with intact ventricular septum	0
12	Tetralogy of Fallot	1
13	Left atrial isomerism, complete atrioventricular septal defect	1
14	Double outlet right ventricle (Taussig-Bing), subvalvular aortic stenosis, hypoplastic aortic arch	1
15	Transposition of the great arteries with intact ventricular septum	0
16	Complete atrioventricular septal defect	1
17	Coarctation of the aorta, hypoplastic aortic arch, ventricular septal defect	2
18	Hypoplastic left heart syndrome (MA/AA)	1
19	Coarctation of the aorta, ventricular septal defect	2
20	Tricuspid atresia with right ventricle hypoplasia, transposition of the great ventricles, ventricular septal defect, coarctation of the aorta, hypoplastic aortic arch	1
21	Transposition of the great arteries with intact ventricular septum	0
22	Pulmonary atresia, Ebstein anomaly	1
23	Transposition of the great arteries with intact ventricular septum	0
24	Tetralogy of Fallot	1
25	Right atrial isomerism, atrioventricular septal defect, pulmonary atresia, transposition of the great arteries	1
26	Right atrial isomerism, atrioventricular septal defect, pulmonary atresia	1
27	Transposition of the great arteries with intact ventricular septum	0
28	Double inlet left ventricle, transposition of the great arteries, interruption of the aortic arch type A	1
29	Transposition of the great arteries with ventricular septal defect	0
30	Unbalanced right-dominant atrioventricular septal defect.	1
31	Double outlet right ventricle, transposition of the great arteries, hypoplastic aortic arch	1
32	Common arterial trunk type I	1
33	Tetralogy of Fallot	1
34	Common arterial trunk type I	1
35	Dysplastic tricuspid valve, atrial septal defect, ventricular septal defect, small left ventricle	2
36	Coarctation of the aorta	2

MA, mitral atresia; AA, aortic atresia. 0 = low cerebral oxygen delivery; 1 = mixed cerebral oxygen delivery; 2 = normal cerebral oxygen delivery.